Is elective percutaneous coronary intervention a thing of the past?

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Take Home Messages

- . Elective PCI has traditionally made up a significant proportion of coronary intervention in the United Kingdom
- COURAGE, ISCHAEMIA and ORBITA are key trials which question the evidence behind elective PCI, demonstrating no improvement in MACE.
- Medical therapy and lifestyle intervention should be first line with judicious use of PCI following informed discussion with patients.

Introduction

The landscape of interventional cardiology has seen seismic shifts over recent years, with traditional treatments such as elective percutaneous coronary intervention (PCI) facing increasing scrutiny. Evolving evidence and an improved understanding of stable coronary artery disease has led to questions around the supposed benefits of this intervention in patients with stable angina [1,2]. This editorial aims to briefly examine the underlying evidence and look to answer the question – is elective PCI a thing of the past?

Traditions and dogma

Elective PCI has traditionally been seen as a cornerstone in the management of stable coronary artery disease (CAD), accounting for a third of coronary interventions in the United Kingdom between 2006-2019[3]. Historically, the use of PCI for stable CAD had rested on the assertion that it improves a patient's symptom burden from angina and reduced their risk of major adverse cardiovascular events (MACE). Whilst revascularisation of angiographically narrowed coronary arteries may appear intuitive, the evidence suggests that it may not be so straightforward, which brings the existing dogma into question.

Evidence

COURAGE was the first trial challenging existing practice, by demonstrating that in 2287 patients with stable angina randomised to either PCI with optimal medical therapy (OMT) or OMT alone, the addition of PCI led to no significant difference in MACE (19.5% for medical therapy vs 20% for PCI HR 1.05, 95% CI 0.87-1.27, p = 0.62)[4]. However, there are several notable limitations including the use of bare-metal stents (now largely not used for high rates of in-stent restenosis) and cross-over rate of 30% into the PCI arm (**Table 1**). Nonetheless, this set about a cascade of trials questioning the role of PCI in stable CAD.

ISCHAEMIA took place in the era of new drug eluting stents (DES) looking at 5179 patients with stable CAD and moderate to severe ischaemia on stress imaging[5]. It randomised patients to an either an initial invasive strategy of angiography and optimal revascularisation with OMT or OMT alone. The study demonstrated no significant difference in MACE between allocation arms (15.5% medical therapy vs 13.3% invasive group, p=0.34), though improvements in quality of life was observed in patients experiencing anginal symptoms (mean 3.7 point higher Seattle Angina Questionnaire score (SAQ) in invasive group. Notably, this study excluded higher risk patients such as those with class III/IV heart failure symptoms, severely impaired left ventricular function and significant left main stem disease. In addition, around 34% of patients did not report anginal symptoms on enrolment[6].

FAME and FAME2 brought in the use of fractional flow reserve (FFR), an invasive physiological assessment of ischaemia, to guide revascularisation decision making [7,8]. In FAME, 1005 patients with multi-vessel CAD were randomised to either angiography guided PCI versus FFR guided PCI . This demonstrated significantly reduced MACE in the FFR group (13.2% vs 18.3%, p = 0.02). Of the angiographically indicated lesions, FFR was negative in about 33% i.e., deemed non-significant. Overall, this led to significantly less stents, use of contrast, cost and hospital stay. FAME 2 went on to compare FFR guided PCI and OMT with OMT alone in 888 patients with ischaemia as defined by FFR <0.8 with or without symptoms. The trial was terminated early as interim analysis demonstrated a clear benefit in the PCI and OMT arm, with significantly lower MACE (4.3% in PCI group vs 12.7% in OMT, HR 0.32, 95% CI 0.19-0.53, p<0.001 which was mainly driven by reduction in urgent revascularisation (1.6% vs 11.1%, p<0.001). There was also significant improvement in CCS angina class from baseline. There were important limitations however with a short mandated follow up (mean duration 7

months) and a cross over rate of 41% from OMT group into the FFR guided PCI arm. DEFINE-FLAIR assessed the use of instantaneous wave-free ratio (iFR) guided PCI compared to FFR in 2492 patients with stable angina or ACS [9]. Functional significance was defined as iFR <0.89 and FFR <0.8. The trial demonstrated no significant difference in MACE (6.8% vs 7%, p<0.001), demonstrating iFR to be non-inferior for functional assessment of indeterminate coronary artery stenosis. The use of iFR led to reduced adverse procedural events, procedure time and cost without need for hyperaemic agent.

Lastly, FAME3 went on to assess whether FFR-guided PCI would be non-inferior to CABG in 1500 patients with three-vessel disease without left main involvement [10]. In the FFR-guided PCI arm, all physiologically significant lesions (FFR <0.80) were stented with current generation drug-eluting stents (DES) whilst in the CABG arm, revascularisation was based on angiographic appearance (with FFR not mandated), using arterial grafts. The trial demonstrated greater MACE in the FFR guided PCI group vs CABG at 1 year (10.6% vs 6.9% with HR 1.5 and CI 1.1-2.2 and p = 0.35). However, at 3-years, the trial demonstrated no difference in MACE between the two groups (12% vs 9.2%, CI 0.98-1.83, p = 0.07) though higher rates of MI (7 vs 4.2%, p = 0.02) and repeat revascularisation (11.1% vs 5.9% p = 0.001). Subgroup analysis went on to suggest that patients with low syntax scores (0-22) may derive most benefit from PCI vs CABG.

ORBITA was the first trial to include a placebo sham procedure and have patients blinded to treatment allocation[11]. In ORBITA, 200 patients with stable angina and at least one angiographically significant lesion (>70%) in a single vessel, were randomised to either PCI with OMT or a sham procedure with OMT. Invasive physiological assessment was performed but not available to operators (i.e. the PCI was angiographically guided, with significance defined as >70% stenosis). The results demonstrate that PCI did not result in improvements in exercise time (28.4 seconds vs 11.8 seconds, p=0.2) or anginal frequency (change in SAQ physical limitation from baseline 7.4 vs 5, p = 0.42) compared to sham procedure in patients with angiographically significant stenoses. Limitations include small sample number (N=200), short follow up duration (6 weeks) and angiographic rather than physiological guidance which may have underestimated benefit of PCI through unnecessary stenting. The initial 6-week optimisation stage was intensive and unlikely replicable in a real-world setting.

Finally, ORBITA-2 went on to assess PCI vs sham procedure in 301 patients with stable angina and at least one anatomically significant coronary artery stenosis on angiography or computerised tomography coronary angiography (CTCA) with evidence of ischaemia on stress echocardiography, perfusion cardiac MRI, myocardial perfusion scan or invasive pressure wire assessment. Patients were taken off anti-anginal medication at enrolment in order to assess the efficacy of PCI alone and only eligible if one or more episodes of angina reported in preceding 2 weeks[12]. The study demonstrated significant reduction in mean angina symptom score for PCI vs placebo (2.9 vs 5.6, OR 2.21, 95% CI 1.41-3.47, p <0.001) which confirms the anti-anginal benefit of PCI. However, there are important limitations, namely the short follow up duration (12 weeks) and small sample size.

Trial	COURAGE	ISCHAEMIA	FAME	FAME2	FAME3	DEFINE-FLAIR	ORBITA	ORBITA-2
Type of study	Randomised parallel trial	Randomised parallel trial	Randomised parallel trial	Randomised parallel trial	Randomised parallel non-inferiority trial	Randomised parallel trial	Randomised control trial	Randomised control trial
Population	Patients with stable CAD with either stenosis >70% in ≥1 proximal epicardial coronary artery with objective evidence of myocardial ischaemia	Patients with stable CAD and moderate-severe myocardial ischaemia on non-invasive stress testing	Patients with multi-vessel CAD (stenosis >50%) in at least 2/3 major coronary arteries	Patients with one of more stenoses with ischaemia (FFR <0.8)	Patients with three vessel disease without left main involvement.	iFR vs FFR guided PCI in patients with stable angina or ACS	Patients with stable CAD with at least one severe coronary artery stenosis	Patients with stable CAD with at least one severe coronary stenosis on CTCA/invasive angiography with ischaemia on non-invasive imaging or invasive coronary physiological test.
Sample size	2287	5179	1005	888	1500	2492	200	301
Intervention	PCI with optimal medical therapy vs optimal medical therapy alone	Routine invasive therapy (angiogram and PCI or CABG as appropriate) versus medical therapy	Angiographically guided vs FFR guided PCI in patients with multi-vessel CAD	FFR guided PCI and OMT compared to OMT alone in patients with ischaemia (FFR <0.8)	FFR guided PCI with latest DES (lesions <0.80) compared to CABG with arterial graft	iFR vs FFR guided PCI	PCI with medical therapy vs sham placebo procedure with medical therapy	PCI compared to placebo procedure. Both groups off all anti-anginal medications.
Findings	No significant differences between groups in composite outcome of death, non-fatal MI, stroke or hospitalisation for ACS (19.5% for medical therapy vs 20% for PCI HR 1.05, 95% CI 0.87-1.27, p = 0.62)	- No significant difference in cardiovascular death, MI, resuscitated cardiac arrest or hospitalization for unstable angina or heart failure ((15.5% medical therapy vs 13.3% invasive group, p=0.34) - Modest improvement in symptom benefit at 3 months amongst daily/weekly angina which persisted at 12-36 months.	No significant difference in MACE for FFR group (13.2% vs 18.3%, p = 0.02)	Significant reduction in MACE in PCI and OMT group (4.3% in PCI group vs 12.7% in OMT, HR 0.32, 95% CI 0.19-0.53, p<0.001 which was mainly driven by reduction in urgent revascularisation (1.6% vs 11.1%, p<0.001)	Higher rates of MACE at 1 year in the FFR guided PCI arm compared to CABG (10.6% vs 6.9% with HR 1.5 and CI 1.1-2.2 and p = 0.35) No difference in MACE at the 3 years (12% vs 9.2%, CI 0.98-1.83, p = 0.07). Higher rates of MI and repeat revascularisation (7 vs 4.2%, p = 0.02 and 11.1% vs 5.9% p = 0.001 respectively)	iFR guided PCI non-inferior compared to FFR with regards to MACE (6.8% vs 7%, p<0.001)	No significant difference between groups in terms of treadmill exercise time. No change in peak oxygen uptake, exercise time to 1mm STD, angina severity (CCS class), physical limitation or angina frequency	PCI led to lower angina symptom score compared to placebo procedure
Limitations	- Unblinded - Predominantly white (86%) men (85%). - Excluded persistent class IV angina, markedly positive stress. - Bare metal stents during PCIs (DES not commonplace at the time) - High cross over rate >30% shifting to PCI group.	- Unblinded - 34% no angina at baseline. - Excluded 'unacceptable angina at baseline'	- Treating clinicians unblinded - Patients recruited with lesions >50% angiographic stenosis not necessarily reflective of clinical practice - Cut off of 0.8 rather than 0.75 leading to PCI of potentially functionally non-significant lesions	- Unblinded - Short mandated follow up (7 months) - Cross over rate of 41% from OMT to FFR guided PCI arm - Trial stopped early after randomising 888 patients (original target 1623)	- 19% women, 93% white - Not explicitly powered for 3-year follow up. - Only 12% of patients assigned to PCI received intravascular imaging, therefore potential for further optimisation.	-	- Excluded patients with multi-vessel disease, impaired LV. - 23-25% CCS 0-1 angina, low-moderate physical limitation on Seattle angina Questionnaire - Short follow up (6 weeks) - Small sample size (N=200)	- Short follow up (12 weeks), - Small sample size (301)

Table 1: Summary of trial evidence. Clinical outcomes utilizing revascularization and aggressive drug evaluation (COURAGE). International study of comparative health effectiveness with medical and invasive approaches (ISCHAEMIA). Fractional flow reserve versus angiography for multivessel evaluation (FAME). Functional lesion assessment of intermediate stenosis to guide revascularization (DEFINE-FLAIR). Objective randomized blinded investigations with optimal medical therapy of angioplasty in stable angina (ORBITA). Myocardial infarction (MI). Acute coronary syndrome (ACS). Drug eluting stent (DES). Coronary artery disease (CAD). Coronary artery bypass graft (CABG). Canadian Cardiovascular society (CCS). Computed tomography coronary angiography (CTCA).

Implications

The evidence suggests a need to rethink the immediate impulse to intervene on coronary lesions i.e. the so called 'oculostenotic reflex'[13, 14]. Firstly, it is important to acknowledge the role of optimal medical therapy, which has made significant strides as part of a robust

prevention strategy and challenges the notion of mechanical intervention as the first line approach for stable CAD[15, 16]. This includes beta-blockers to reduce heart rate and thus demand ischaemia, lipid lowering therapy, anti-platelet therapy and control of blood pressure and diabetes. It is the only therapy that has been demonstrated to improve prognosis in patients with stable CAD regardless of revascularisation status [17, 18, 19]. Secondly, the emergence of physiological based assessment has recalibrated the threshold for intervention and takes away the subjective nature of angiographic based assessment. Overall, whilst there is compelling data against the use of elective PCI for reducing MACE, there is evidence that a subset of patients will derive meaningful benefits, particularly those with refractory symptoms despite optimal medical therapy [20]. This puts the onus back on the physician-patient relationship and an informed discussion about risks and benefits.

Conclusion

In conclusion, while the proclamation of the end of elective PCI may sound audacious, it reflects a deeper understanding and a shift in approach to stable coronary artery disease. Ultimately, medical therapy and lifestyle intervention will remain the cornerstones, with the evidence suggesting a more nuanced and judicious approach to the use of PCI which is guided by physiology and after an informed discussion of the risks and benefits with the patient.

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